(PF490) CHIDAMIDE PLUS VENETOCLAX AND AZACITIDINE (VAC) VERSUS VA REGIMEN IN NEWLY DIAGNOSED IMMUNOPHENOTYPICALLY MATURE MONOCYTIC AML: AN UPDATED ANALYSIS FROM A MULTICENTER RANDOMIZED STUDY

Topic: 04. Acute myeloid leukemia - Clinical

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Background

While the combination of Venetoclax and Azacitidine (VA) has become the first-line induction regimen for newly diagnosed AML patients who are ineligible or decline intensive chemotherapy, resistance remains a critical challenge. Mature monocytic differentiation has been identified as a key driver of resistance to BCL-2 inhibition (Pei S et al. *Cancer Discov*, 2020), suggesting the need to target the specific subgroup the mature monocytic AML subgroup. Since monocytic lineage leukemia cells show susceptibility to histone deacetylase inhibitors (HDACi), we hypothesized that incorporating Chidamide, a selective HDACi, into the VA regimen (VAC regimen) could overcome resistance.

Aims

To evaluate the updated efficacy and safety of VAC versus VA regimens in a larger cohort of unfit patients with immunophenotypic monocytic AML.

Methods

In this multicenter study (NCT05566054), we screened and enrolled patients with newly diagnosed Im-Mono AML, defined by strict flow cytometry criteria that promonocytes positive for more than 2 monocytic markers (CD11b, CD14, CD36 and CD64) and negative for CD34 or CD117. Patients were treated with either the VA regimen (Azacitidine 75mg/m^2 on d1-d7 and Venetoclax at an escalated dose of 100mg, 200mg and 400mg by day 28) or the VAC regimen (VA + Chidamide 10mg/d for d1-d7). This analysis compares the updated clinical outcomes between the two arms. The primary endpoint was the composite complete remission rate (CRc). Secondary endpoints included MRD negativity (defined as $<1\times10^{-3}$ by flow cytometry), overall survival (OS), and adverse events (AE).

Results

Clinical data cutoff was September 2025, a total of 80 patients with ND Im-Mono AML disease by flow criteria were enrolled. 40 patients received the VAC regimen and 40 patients received the VA regimen. There were no significant difference in baseline characteristics between the two groups of patients (P>0.1). At the end of 1 cycle of treatments, the CRc in the VAC group was 70.0%, which was significantly higher than the 47.5% in the VA group (P=0.041).

The MRD-negative CR rate in the VAC group was 82.1% and the VA group was 73.7% (P=0.740). At a median follow-up of 12.6 months (range, 0.8-32.1), median OS was not reached in either group. The 2-year OS rates were 63.9% for VAC versus 56.4% for VA. Importantly, the addition of Chidamide did not increase toxicity, with comparable incidences of grade ≥3 neutropenia, thrombocytopenia, and transfusion dependence between arms (all P>0.05). *In vitro*, dual BCL-2/HDAC inhibition synergistically targeted the distinct metabolic dependencies of monocytic blasts.

Summary/Conclusion

This updated analysis substantiates the clinical benefit of the VAC regimen over standard VA therapy for Im-Mono AML. By specifically targeting the monocytic differentiation resistance mechanism, the triple combination significantly enhances remission rates and response depth without compromising safety. These findings advocate for differentiating AML subtypes by immunophenotype to guide precision combination therapies.

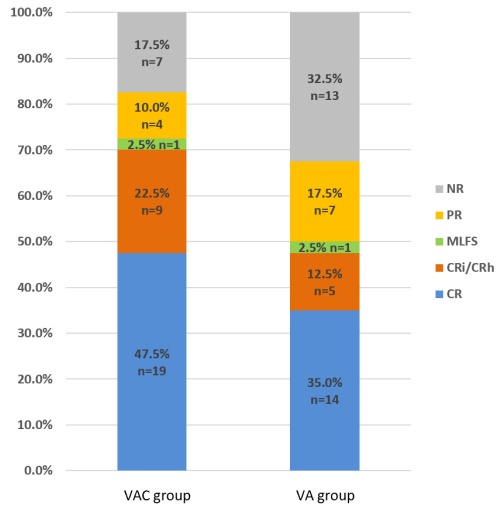

Figure 1. Efficacy of VAC versus VA regimen.

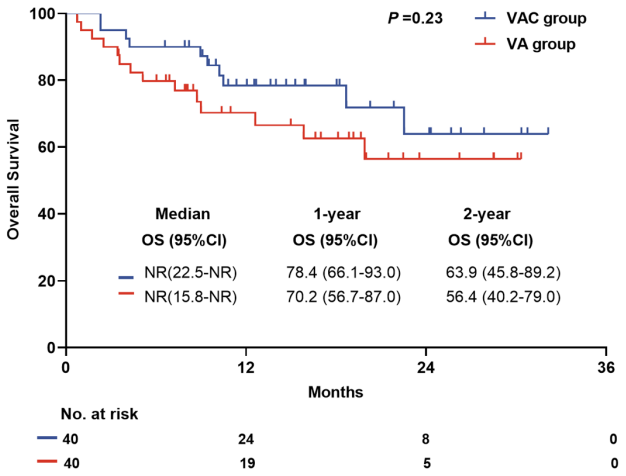

Figure 2. Overall survival of of patients treated with VAC regimen versus VA regimen.